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# Childhood Cancer Etiology: Recent Reports

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## Cars and Childhood Leukemia: Isolating Circumstances

Alexander et al. recently reported the results of an ecologic study examining the relationship between car ownership and childhood acute lymphoblastic leukemia (ALL) in England and Wales [Paediatric and Perinatal Epidemiology 10:411–417, 1996]. The analysis included 438 children under the age of 14 diagnosed with ALL between 1984–1989. The data obtained for the 3,270 electoral wards included in this analysis were: proportion of households without a car, a measure of isolation from the nearest 'built up' area, and an indicator of socioeconomic status. Overall, no relationship was found between car ownership and childhood ALL. However, after adjustment for car ownership, there was a statistically significant association between increased isolation and increased rates of childhood ALL.

### COMMENT

A previous analysis of this same data set found a statistically significant relationship between geographic isolation and childhood ALL [Alexander et al., Lancet 336:1461–1465, 1990]. In that analysis, they suggested that the increased rates of childhood ALL in isolated wards were due to different patterns of exposure to infectious agents for children living in these areas. In the current study, they explored an alternative explanation for the original finding, namely that increased exposure to benzene in gasoline fumes led to the increased rates in the isolated areas. In other words, the authors took the refutational or Popperian approach to exploring their hypothesis. Advocates of this school of thought believe that science will advance more rapidly if researchers actively explore alternative hypotheses rather than replicating previous findings. Although this ecologic analysis has some weaknesses, it is a breath of fresh air due to the ingenuity of its approach.

Adrine R. Swensen

## ALL—Is JC Virus to Blame?

A great deal of epidemiological effort has been directed toward understanding the age peak of childhood ALL that occurs in developed countries in the 2–5 year age range. This incidence peak is associated with a specific leukemia phenotype (common ALL (cALL); i.e., early B-precursor ALL expressing the CD10 surface antigen) and appears to be a recent phenomenon, not being apparent in the early years of this century. It has been hypothesized previously (''Greaves hypothesis'') that cALL arises as a rare response to a common childhood infection. This hypothesis proposes that in countries with higher living standards, children are less likely to be exposed to common infectious agents during infancy and that subsequent infection later in childhood leads in rare instances to cALL. In this paper, Malcolm Smith [Immunotherapy 20:89–100, 1997] presents the case for JC virus as an etiologic candidate for this infective agent. JC virus meets the criteria one would expect for an infectious exposure that might cause cALL in this way. JC virus is a polyoma virus with a predilection for B lymphocytes. Infection is ubiquitous in the human population with approximately 50% of pregnant women seropositive. Infection with JC virus occurs earlier in developing countries and populations with lower socioeconomic conditions and primary infection is generally not associated with clinical symptoms. JC virus has been shown to be oncogenic in animal models (associated with astrocytomas, neuroblastomas, and PNET). The JC virus T antigen also associates with p53 and can induce genomic instability by this mechanism.

### COMMENT

The case for JC virus is presented carefully and plausibly in this hypothesis paper. Of importance is the fact that this is a testable hypothesis, and the paper lists 10 predictions of the model, some of which will be amenable to study. It is worth noting, however, that convincingly demonstrating the role of a ubiquitous virus in etiology can be challenging. Somewhat analogous observations of SV40 viral DNA sequences (initially introduced into the human population in polio vaccine) in some childhood brain tumors are provocative and intriguing. However, proving that the viral sequences contribute to

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etiology (or are transcriptionally or otherwise active) is proving difficult.

Stella M. Davies

### Childhood ALL: Is There a Bug in the System?

It has long been speculated that childhood acute lymphoblastic leukemia (ALL) may be the direct result of a yet unidentified viral agent. Alternatively, an unusual exposure to a common infection may initiate or promote ALL. As potential candidate viruses remain elusive, researchers must use indirect methods to determine if the patterns of occurrence of childhood ALL are suggestive of an infectious etiology. Recent studies have taken dramatically different approaches to investigate this hypothesis.

Meltzer et al. [Leukemia and Lymphoma 23:85–92, 1996] investigated the relationship between month-of-birth and the incidence of ALL in children. They hypothesized that an association between birth month and incidence of ALL would provide supportive evidence of the role of a periodically virulent viral infection in the development of childhood ALL. Towards this end, they analyzed a large SEER data set containing 2,380 children diagnosed from 1973–1986. Overall, they found no relationship between month of birth and incidence of ALL in children. Furthermore, there was no evidence of seasonality.

Alexander et al. [British Journal of Cancer 75:457–463, 1997] examined the patterns of occurrence of childhood leukemia in Hong Kong from 1984–1990. Over the past 3 decades in Hong Kong, new towns have been developed in previously rural areas to accommodate the expanding population. This mass internal migration may result in a change in exposure patterns to infection. The authors hypothesize that this population mixing may result in clustering of childhood ALL. This population-based study found evidence of geographical clustering within small areas for children diagnosed between the ages of 0 and 4 ($P = 0.09$). When analyses were restricted to those areas with extreme population mixing, the evidence for clustering was even more compelling ($P < 0.0007$). Hence, the results of this study provide support for the infectious etiology of childhood ALL and are compatible with findings from analyses conducted in the United Kingdom.

### COMMENT

Many different approaches have been used to investigate the possibility of a viral etiology for childhood ALL. They have included, but are not limited to, the analysis of clusters, seasonality, birth order, and day-care attendance. Although the composite results of these studies are still inconclusive, the data are sufficiently impressive that it is important to continue the search for the elusive ''bug'' that may play a role in the development of childhood ALL. The ability to explore the relationship between the patterns and distributions of incidence and potential exposures is one of the main strengths of epidemiology, as evidenced by the determination that AIDS was the result of an infectious agent before HIV was identified.

Andrine R. Swensen

### Cancer In Twins: Is Dolly More Than Just Her Genes?

Twin studies can be quite informative in attempting to tease out the contributions of the environment vs. genetics. In a recent study in Sweden by Ahlbom et al. [JNCI 89:287–293, 1997], both monozygotic and dizygotic twins were studied to determine cancer outcome and mortality. Two groups were investigated: 1) twins who were born between 1886 and 1925 (''old cohort''), and who were both alive at the time the Swedish Twin Registry was established in 1959–1961; and 2) twins who were born between 1926 and 1958 (''young cohort'') who were both alive, living in Sweden in 1970, and who completed a questionnaire in 1972 (same-sex pairs only). These twin records were linked to the Mortality Registry of Statistics and the Swedish Cancer Registry. Of the old cohort, over 41,000 twin pairs were born during this time, 12,889 were both still alive, and 10,503 completed a questionnaire (previously validated) that determined monozygosity. Of these ''old cohort'' pairs, 3,617 cases of malignancy were identified. Of the young cohort, 12,883 same-sex pairs completed the questionnaire, and 918 cases of malignancy were identified. A familial influence on cancer risk can reflect either shared genes (heritable component) or shared environment. Heritability was assessed by comparing monozygotic (MZ) vs. dizygotic twins (DZ). When all cancers were combined, there was a clear familial effect for both males and females that was mostly explained by a heritable rather than environmental component for both the old and young cohorts. For individual cancer sites, familial effects were noted for stomach cancer, colorectal cancer, lung cancer (males), breast cancer (females), cervical cancer, and prostate cancer. Of these, heritability was ascribed to colorectal cancer in males, breast cancer, cervical cancer, and prostate cancer by comparison of monozygotic and dizygotic pairs.

### COMMENT

This twin study addressed familial associations in adult cancer. Due to the overall low incidence of childhood cancer in the population it would be difficult to assess these differences with any great certainty in young twins. However, it is widely recognized that there is a

high degree of concordance for leukemia in monozygotic infant twins, which precipitously drops with increasing age [Strong LC.: In Sutow WW, Fernbach DJ, Vietti TJ, (eds): Clinical Pediatric Oncology. CV Mosby: St. Louis, MO, 1984]. There is speculation that this high concordance results from the transfer of leukemic cells in shared placental circulation and there are molecular data to support this theory [Ford et al., Nature 363:358–360, 1993].

Even with the rigorous statistical examination of teasing out environmental from genetic factors in the study by Ahlbom et al., it was apparent that the relative risks for MZ twins vs. DZ twins (mostly on the order of 1.5–2.0) were not that much more compelling than what is generally obtained in an environmental risk factor study. This study was nicely done, and it does argue that certain individuals likely possess a genetic susceptibility to cancer at a particular site. However, it also supports the notion that we (as well as any clone we may encounter) are more than just our genes.

Julie A. Ross

### Birth Defects in Children With Cancer: Genetic Events in Common?

Past research in children with cancer and congenital anomalies has shown that some associations are attributable to known contiguous-gene syndromes, but the mechanism for most such occurrences is still unknown. In this study, the records of 20,304 children registered into the British National Registry of Childhood Tumors (NRCT) between 1971 and 1986, were examined. Information on the presence of congenital anomalies was obtained at the time of confirmation of the cancer diagnosis, and from a postal questionnaire sent to the family physician. The observed number of children with cancer of a specific type and a particular congenital anomaly was compared with: 1) the expected number based on the frequency of the anomalies among children in the entire study, and 2) the expected number based on the frequency of anomalies recorded in the British Columbia Health Surveillance Registry (BC Registry). Since the purpose was to identify new associations of malformations and cancer, known associations were excluded (275 cases with Down syndrome, tuberous sclerosis, neurofibromatosis, Wilms/aniridia syndrome, immunodeficiency syndromes, and other chromosomal defects). After these exclusions (which constituted 45% of all anomalies found in children with leukemia) the frequency of anomalies was much higher among children with solid tumors (4.4%) than among those with leukemia or lymphoma (2.6%). The highest rates of anomalies were found in Wilms tumor (8.1%), Ewing sarcoma (5.8%), hepatoblastoma (6.4%), and gonadal and germ cell tumors (6.4%). Also, children with cancer had a higher occurrence of spina bifida and abnormalities of the eyes, ribs and spine, than population-based controls. [Narod SA et al., American Journal of Human Genetics 60:474–485, 1997].

## COMMENT

Epidemiologic reports as early as 1968 have suggested that infants and children with specific chromosome abnormalities have increased risks of childhood cancers. Since then, studies have searched other types of childhood cancer and congenital abnormalities, and have documented associations such as Wilms tumor and aniridia, as well as leukemia and Down syndrome, neurofibromatosis, and ataxia telangiectasia. This research benefits greatly from the availability of a population-based registry for comparison purposes. Population-based studies such as this one are useful in furthering investigations into possible un-recognized associations between large groups of congenital anomalies and malignancy. The further report of an excess of rib and vertebral anomalies is fascinating and has been reported previously [Schumacher et al., European Journal of Pediatrics, 151:432–434, 1992; and McKeen et al., New England Journal of Medicine 309:1522, 1983]. As the authors point out, this may indicate an abnormality of genes controlling pattern formation and segmentation (homeobox genes), a family of genes that have also been implicated in carcinogenesis [Kennedy et al., PNAS 88: 8900, 1991] and warrant further study.

Ann C. Mertens

### Big Isn't Always Better

Simpson-Golabi-Behmel Syndrome (SGBS) is an X-linked condition characterized by pre- and postnatal overgrowth. Affected males often attain heights over 6 1/2 feet and have a distinctive facial appearance. Additional clinical findings observed in individuals with SGBS are congenital heart defects, enlarged and dysplastic kidneys, cryptorchidism, hypospadias, hernias, supramammary nipples, vertebral and rib abnormalities such as the Klippel-Feil anomaly, and postaxial hexadactyly. These patients are also at high risk for development of embryonal tumors, and an excess of Wilms tumor and neuroblastoma in early childhood has been reported. There is some variability in the mental development of affected males but most appear to have normal intelligence. The SGBS syndrome has only recently been delineated and these patients are frequently incorrectly diagnosed with Beckwith-Wiedemann syndrome. These two syndromes share many clinical findings and it is often the X-linked pattern of transmission in the SBGS families that allows clear distinction between them. A paper by Pilia et al. [Nature Genetics 12:241–247, 1996] describes the identification of the gene involved in

SGBS. The gene was identified by characterization of breakpoints in two female patients with an X autosome translocation. The gene that has been identified is termed GPC3 and is a glypican gene (a family of genes encoding integral membrane proteins). The gene appears to be selectively expressed in embryonic mesodermal tissues, particularly those affected by overgrowth in SGBS. The authors postulate from Western and ligand-blotting experiments that GPC3 forms a complex with insulin-like growth factor 2 and may exert its phenotypic and cancer-producing effects by modulating IGF-2 action.

## COMMENT

Abnormal regulation of IGF-2 through alterations in imprinting has been suggested as a causative factor in the tissue overgrowth and tumor excess seen in Beckwith-Wiedemann syndrome. Identification of this new gene suggests that SGBS may be similarly due to abnormal IGF-2 regulation, with the dysregulation being achieved through a different pathway.

Stella M. Davies

### Hodgkin Disease—Are Women Getting Ahead?

Data from the Connecticut tumor registry indicate a startling increase in the incidence of Hodgkin disease (HD) over the past 60 years, with the most dramatic increase occurring in females since 1970. Age adjusted annual incidence rates for females were 1.63/100,000 in 1935–1939, 2.5 in 1960–1964, and 3.78 in 1990–1992; for males rates were 2.3, 3.8, and 4.4 at the same time-points. For patients younger than 20 years, incidence rates were lower than for older patients; rates have increased slightly over time but have decreased recently for both males and females. Rates have changed most in patients 20–44-years-old and over 45 years of age. Before 1970, rates increased for both ages. After 1970, incidence rates continued rising in young adults between 20 and 44 years, and the increase was much more dramatic in women. The authors estimate an 11% increase in incidence per 5 years for women. In adults older than 45, between 1970 and 1992, rates decreased and were lower than those of young adults ages 20–44. For both sexes, nodular sclerosis was the predominant histologic type in the 20–44-year-old group and was the major contributor to the rise, especially for women. The authors used statistical methods to examine the data for a period effect (likely to reflect improvements in diagnosis) and for a birth cohort effect (likely to reflect changes in environmental exposures) and found evidence of a cohort effect. The authors discuss lucidly possible explanations for the data, and reject known HD risk factors (EBV infection, HIV infection, improving socioeconomic status) as likely explanations. Influenced particularly by the gender disparity and by indirect evidence that reproductive factors play a role in HD, the authors speculate that changing social trends in reproduction may be the explanation. Previous epidemiologic studies have shown reduced risk of HD with marriage, higher parity, and less than 30 years of age at first pregnancy. Fertility data for Connecticut indicate later age at first pregnancy and reduced parity since 1960, supporting this theory. [Chen et al., Cancer 79:2209–2218, 1997].

## COMMENT

The Connecticut tumor registry is the oldest population-based tumor registry in the world and the perspective that 60 years of carefully collected data can provide is illuminating. The striking temporal trend in young females offers an important opportunity to identify possible causes of Hodgkin disease, information that will be useful to both pediatric and adult oncologists.

Stella M. Davies